Physiology-Guided CPR

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KEYWORDS

• Cardiopulmonary resuscitation • Cardiac arrest • Physiology • Blood pressure
• End-tidal carbon dioxide

KEY POINTS

- Current guideline-recommended cardiopulmonary resuscitation (CPR) targets are provider-centric and importantly do not adapt in real-time based on patient physiologic response.
- Physiology-guided CPR represents a shift toward precision resuscitation, aiming to optimize outcomes by adapting CPR techniques in real-time based on individual patient physiology.
- Key physiologic markers, including arterial blood pressure and end-tidal carbon dioxide, are associated with survival outcomes; specific targets and practical implementation strategies remain key knowledge gaps.

INTRODUCTION

Cardiac arrest, defined as the abrupt and complete cessation of blood flow and meaningful myocardial function, strikes over 400,000 people annually in the United States.[1–3] Survival to hospital discharge for out-of-hospital cardiac arrest (OHCA) is around 10% in both adults and children, with survival to hospital discharge for in-hospital cardiac arrest (IHCA) around 25% in adults and 50% in children.[1–5] Prompt initiation of cardiopulmonary resuscitation (CPR) remains the cornerstone of treatment for both OHCA and IHCA, with numerous studies demonstrating that prompt delivery of CPR is associated with a higher probability of survival.[6–8] Furthermore, this relationship is exquisitely time-sensitive; survival falls by 10% to 15% for each minute CPR is delayed.[9]

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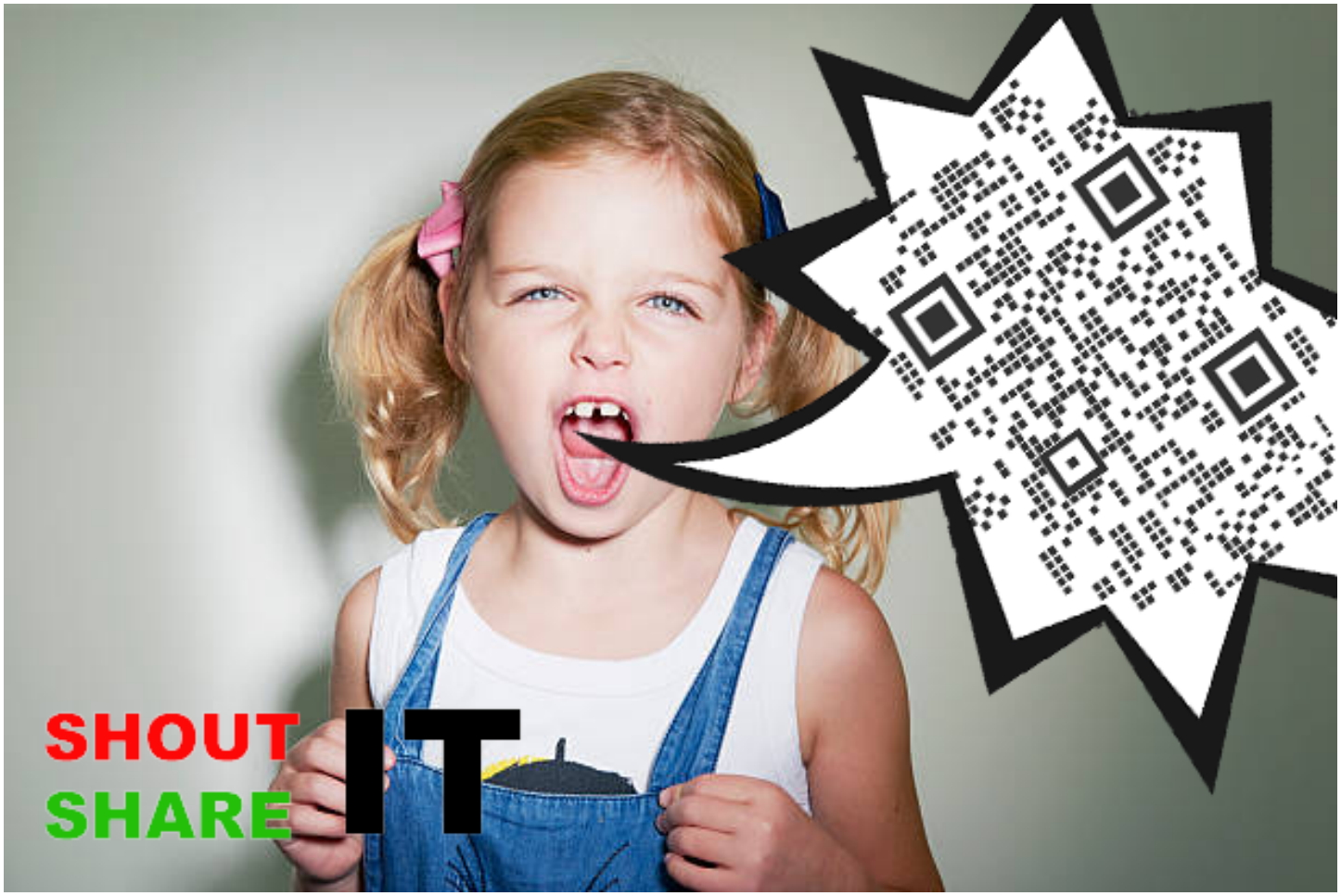
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Abbreviations	
AMSA	Amplitude Spectrum Area
AUCp	area under the curve
CoPP	coronary artery perfusion pressure
CPR	cardiopulmonary resuscitation
DBP	diastolic blood pressure
ECG	electrocardiogram
$ETCO_2$	end-tidal carbon dioxide
IHCA	in-hospital cardiac arrest
MAP	mean arterial blood pressure
NIRS	near-infrared spectroscopy
OHCA	out-of-hospital cardiac arrest
POCUS	point-of-care ultrasound
PPV	positive-predictive value
RAP	right atrial diastolic blood pressure
ROSC	return of spontaneous circulation
rSO2	regional oxygen saturation
SBP	systolic blood pressure
TEE	transesophageal echocardiography
TTE	transthoracic echocardiography
VF	ventricular fibrillation

CPR is a fundamental intervention in cardiac arrest resuscitation, yet the clinical impact of CPR is highly dependent on the quality of CPR delivered. Numerous laboratory and clinical studies have demonstrated that intra-arrest hemodynamics and survival outcomes vary considerably with such factors as chest compression rate,[10] depth,[11] chest recoil between compressions[12] (i.e. to what extent rescuers "lean" on the sternum between compressions), and compression fraction[13] (i.e. the percentage of time during which compressions are delivered). Widespread variability in CPR quality has been documented in clinical investigations,[14–16] despite international resuscitation guidelines and extensive global CPR training infrastructure.

While the "real-world" implementation of resuscitation guidelines to ensure CPR quality represents a challenge, another weakness exists in the current approach: current CPR quality standards are based on performance metrics of the rescuer providing CPR rather than the response of the patient to those efforts. A core principle of critical care is the adjustment of therapy to physiologic endpoints that reflect patient response (e.g. titrating vasopressor dosing to mean arterial pressure, or tuning fraction of inspired oxygen to hemoglobin saturation), yet this is not standard practice in cardiac arrest resuscitation. For example, current guidelines recommend a compression rate between 100 and 120 per min.[2,3] This recommendation applies to all adults and pediatric patients regardless of underlying physiology, height or weight, cause of arrest, or most importantly, physiologic response to compressions. This standardized approach has facilitated widespread CPR training and practice across laypeople, pre-hospital personnel, and hospital-based clinicians, but in settings in which physiologic monitoring is available, a more tailored and informed approach to CPR holds promise to save more lives. Indeed, in the words of critical care giant Max Harry Weil, rescuers are "flying blind" during CPR delivery without real-time assessment of physiologic response.[17] This is particularly important for IHCA resuscitation, in that hospitalized patients who suffer arrest do so with widely different underlying pathophysiology and as such, the response to CPR and other resuscitative therapies may vary considerably.

Growing data suggest that several physiologic measures may be useful in the guidance of CPR. In this article, we discuss the physiologic basis, supporting evidence,

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advantages, and disadvantages for several candidate physiologic measures that have been studied in the context of CPR delivery (**Table 1**). We then discuss physiology-directed CPR and the research and innovation necessary to bring it to the bedside.

DISCUSSION

Candidate Physiologic Markers During Cardiopulmonary Resuscitation

Invasive arterial blood pressure

Physiologic premise. Achieving return of spontaneous circulation (ROSC) is dependent on attaining adequate myocardial blood flow and thereby myocardial oxygen delivery, with coronary artery perfusion pressure (CoPP) being the hemodynamic determinant of myocardial blood flow. As coronary perfusion occurs during diastole, or the relaxation phase of chest compressions, CoPP can be calculated by the aortic diastolic blood pressure (DBP) minus the right atrial DBP (RAP) [CoPP = DBP – RAP]. Although achieving adequate CoPP during CPR is critical for achieving ROSC, its calculation requires both an invasive arterial blood pressure monitor to measure DBP and a central venous pressure monitor to estimate RAP. In clinical practice, either measuring CoPP or using DBP alone as a surrogate for CoPP are reasonable (**Fig. 1**).[6] Though less well-studied, measurement of systolic blood pressure (SBP) and mean arterial blood pressure (MAP) during CPR may also have physiologic relevance, particularly since MAP is the driving pressure for cerebral perfusion.

Associations with cardiopulmonary resuscitation quality and outcomes. The association between higher CoPP and DBP and survival outcomes has long been established in animal models,[18,19] with CoPP less than 15 to 20 mm Hg predictive of unsuccessful resuscitation.[20,21] Vasopressor administration has been shown to increase SBP, DBP, and CoPP in animal studies and limited human literature,[22–24] and deeper compressions are associated with higher SBP and, in at least 1 study, DBP.[25,26]

The first clinical study associating CoPP with survival outcomes was published in 1990 by Paradis, and colleagues. In 100 adults with OHCA or IHCA in the Emergency Department, initial CoPP and maximal CoPP were significantly higher in patients with ROSC. They found that a CoPP $\geq$15 mm Hg had a positive-predictive value (PPV) for ROSC of 57%, CoPP $\geq$25 mm Hg had a PPV for ROSC of 79%, and no patients with a maximal CoPP less than 15 mm Hg achieved ROSC. Thus, higher CoPP was necessary, but not sufficient for achieving ROSC.[27] Although higher arterial blood pressures (SBP, MAP, and DBP) and greater difference in arterial and venous pressures are associated with ROSC,[28,29] specific intra-arrest blood pressure targets have yet to be established in adults.[2]

In children, a multicenter prospective observational study of 164 patients with IHCA and invasive arterial blood pressure monitoring found that mean DBP $\geq$25 mm Hg in infants (<1 y) and $\geq$30 mm Hg in children ($\geq$1 y) was associated with improved survival to hospital discharge and survival with a favorable neurologic outcome.[30] Cubic spline analysis was then used to evaluate the optimal DBP target for survival and was found to be 27 mm Hg in infants, and 34 mm Hg in children, similar to the *a priori* identified targets. Interestingly, exploratory SBP thresholds ($\geq$60 mm Hg in infants and $\geq$80 mm Hg in children) were not significantly associated with survival or survival with favorable neurologic outcomes. The DBP targets were then validated in a larger prospective multicenter cohort of 413 children, and it was again found that DBP $\geq$25 mm Hg in infants and $\geq$30 mm Hg in children was associated with improved ROSC and survival to hospital discharge.[31]

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Table 1
Candidate physiologic markers during cardiopulmonary resuscitation and their physiologic basis, advantages, disadvantages and identified targets

Candidate Physiologic Marker	Physiologic Basis	Advantages	Disadvantages	Identified Targets
Invasive arterial blood pressure	Coronary artery perfusion pressure (CoPP) determines myocardial blood flow and oxygen delivery. Diastolic blood pressure (DBP) is a reasonable surrogate of CoPP.	Established association with return of spontaneous circulation and survival outcomes	Invasive, requires arterial line	CoPP >20 mm Hg DBP $\geq$25 mm Hg in infants (<1 y) and $\geq$30 mm Hg in children (1–18 y)
End tidal carbon dioxide ($ETCO_2$)	Indirectly reflects cardiac output	Broadly applicable to all patients with invasive airway	Affected by changes in minute ventilation and drug administration (e.g. epinephrine, sodium bicarbonate)	$ETCO_2$ $\geq$20 mm Hg
Cerebral oximetry	Marker of cerebral oxygen delivery	Noninvasive	Value reflects composite measure of vascular compartments; impacted by extracerebral factors; no established targets	rSO2 >50%? Trends likely more valuable than thresholds
Cardiac ultrasound/ echocardiography	Identification of reversible causes of arrest Determination of underlying cardiac activity Optimization of CPR technique	Noninvasive Identification of area of maximal compression and possible left ventricular outflow tract obstruction	Requires specialized training for image acquisition and interpretation Longer CPR pauses	N/A
Pulse-oximeter plethysmography	Waveform characteristics indicative of perfusion	Noninvasive and ubiquitous (in and out of hospital)	No real-time interpretation and use	TBD
Electrocardiogram/ventricular fibrillation waveform	Waveform characteristics indicative of myocardial physiology and metabolism	Optimize likelihood of defibrillation success	Limited data supporting real-time clinical use	N/A

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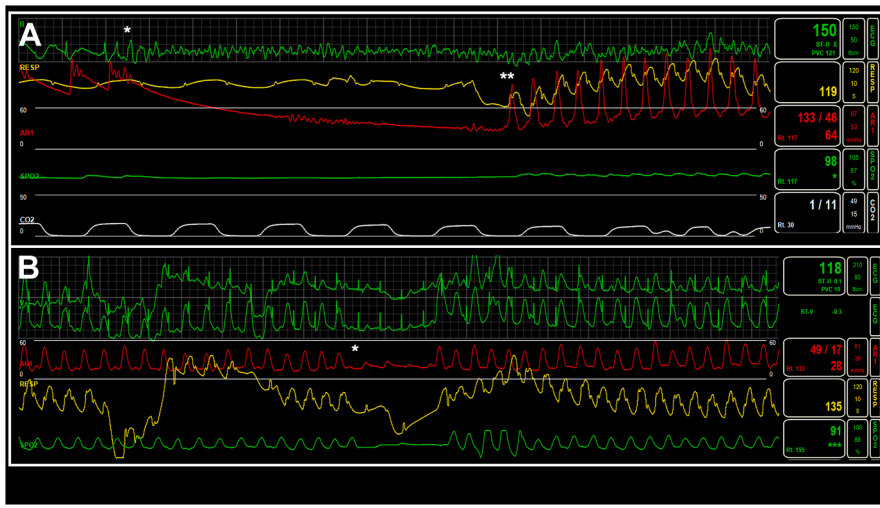

Fig. 1. Intra-arrest Physiologic Waveforms: Two representative bedside monitor recordings of physiologic waveform data during in-hospital CPR. In A, the patient initially has a perfusing rhythm and develops ventricular fibrillation (denoted by *asterisk*) with loss of pulsatility on the arterial line. Quantitative end-tidal CO_2 values decrease with ongoing VF. With commencement of CPR (denoted by *double asterisk*), the efficacy of chest compressions can be seen through increasing systolic and diastolic blood pressures. In B, CPR is ongoing for a patient with pulseless electrical activity. During an interruption in compressions (denoted by *asterisk*), the underlying normal sinus rhythm can be seen but minimal pulsatility and very low blood pressure on the arterial BP tracing prompts continued CPR. Note the low DBP during CPR in this patient.

Blood pressure-directed cardiopulmonary resuscitation. Multiple studies in swine models of IHCA have shown that blood pressure-directed CPR (i.e. compression depth titrated to SBP and vasopressors titrated to CoPP and/or DBP) improved survival outcomes.[32–36] Notably, compared to the standard guideline-directed CPR the blood pressure-directed CPR subjects required shallower depth of chest compressions and more doses of vasopressors prior to defibrillation.[33–36]

To date, there are no interventional clinical trials of blood pressure-directed CPR. A cluster-randomized trial of a bundle of physiology-focused point-of-care training and post-arrest debriefing did not improve outcomes from pediatric IHCA.[37] A propensity-score matched registry study of 23,429 adults with IHCA with an invasive airway or arterial catheter in place at the time of arrest found that clinician-reported physiologic monitoring of CPR quality (either continuous end-tidal carbon dioxide [$ETCO_2$] or DBP) was associated with improved rate of ROSC compared to no reported physiologic monitoring.[38] A similar pediatric study failed to find an association between reported DBP/$ETCO_2$ monitoring and ROSC.[39]

Guideline recommendations. The most recent 2020 AHA adult life support guidelines recommend that it may be reasonable to use physiologic parameters to optimize CPR quality, but do not give recommendations for specific arterial blood pressure targets, citing inadequate clinical data.[2] The 2020 AHA pediatric life support guidelines similarly state that it may be reasonable to use DBP to monitor CPR quality.[3]

Limitations. The main limitation of blood pressure as a physiologic marker of CPR quality is that it requires an invasive arterial monitor. In the prehospital setting, arterial

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lines are uncommon, but have been shown to be feasible.[40] More IHCAs occur in the intensive care unit than the general wards for both adults and children[41,42]; arterial lines are present in just over 10% of adult IHCAs and nearly half of pediatric ICU IHCAs.[37,38] Importantly, the optimal blood pressure targets remain a key knowledge gap for both adults and children, and there are no clinical interventional trials comparing specific blood pressure targets.

End-tidal carbon dioxide

Physiologic premise. $ETCO_2$ has an established role during cardiac arrest as a means of confirming proper advanced airway placement, but has further evolved into a valuable, real-time feedback tool in the management of resuscitation (see **Fig. 1**).[43,44] While $ETCO_2$ is typically most reflective of ventilation during spontaneous circulation,[45] in the low-cardiac output state of CPR,[46] pulmonary blood flow is the major determinant of $ETCO_2$.[45–47] Thus, $ETCO_2$ indirectly reflects cardiac output generated by CPR, and therefore is an important physiologic metric during resuscitation.[6] Importantly, $ETCO_2$ is a more ubiquitous physiologic monitor than invasive arterial blood pressure as about one-third of adults and more than half of children with IHCA have $ETCO_2$ monitoring during arrest.[1,37]

Associations with cardiopulmonary resuscitation quality and outcomes. In adults, significantly higher $ETCO_2$ values are observed in patients with ROSC and survival to hospital discharge[48,49] with variability in the threshold evaluated, but $\geq$20 mm Hg being relatively consistently associated with improved outcomes.[48] Low $ETCO_2$ levels, particularly less than 10 mm Hg throughout CPR or late in resuscitation, are strongly associated with poor outcomes.[44,48,50] The dynamic trend of $ETCO_2$ may also be an important metric, with a positive $ETCO_2$ trend being associated with improved rates of ROSC, survival, and favorable neurologic outcome.[51,52] In a multicenter study of 583 adult OHCA and IHCA events, deeper chest compressions were associated with higher $ETCO_2$ values,[53] supporting a potential means by which clinicians can target $ETCO_2$ during CPR. In children, a prospective multicenter observational study of 234 patients with IHCA found that events with average $ETCO_2$ $\geq$20 mm Hg in the first 10 min of CPR was associated with higher rates of ROSC and survival to hospital discharge. Of note, there was no association between $ETCO_2$ less than 10 mm Hg and worse outcomes in children.[54]

Beyond survival and CPR quality associations, an abrupt increase in $ETCO_2$ is often observed as ROSC occurs,[55–58] which may be useful in identifying underlying ROSC during CPR. In animal models, low-$ETCO_2$ levels from cardiac arrest increase slightly with effective CPR, but increase to normal or even higher than normal levels with ROSC.[59] In a study of 518 adult patients with OHCA who received defibrillation, $ETCO_2$ rose in most patients immediately following defibrillation, and patients with sustained ROSC experienced larger increases in $ETCO_2$.[60] Additionally, the $ETCO_2$ capnogram waveform offers information about resuscitation quality. Oscillations in the capnogram indicate the degree of airway closure and can be used to calculate an airway opening index.[61,62] Airway opening index shows promise as an indicator of the adequacy of ventilation and overall respiratory support during CPR and higher values are associated with higher rates of ROSC.[62]

End tidal carbon dioxide-directed cardiopulmonary resuscitation. Despite considerable data demonstrating an association between higher $ETCO_2$ values and ROSC, there are limited data supporting $ETCO_2$-directed CPR. In porcine models of pediatric cardiac arrest, $ETCO_2$-directed CPR (chest compression rate and epinephrine dosing frequency altered based on $ETCO_2$) resulted in higher $ETCO_2$ values and hemodynamics.[63] In one

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study, this technique also resulted in higher rates of ROSC.[64] There are no published clinical interventional studies of $ETCO_2$-directed CPR.

Guideline recommendations. The American Heart Association life support guidelines for adults and pediatrics both support that $ETCO_2$ may be reasonable to monitor to optimize CPR quality and that it may be an early sign of ROSC.[2,3] The adult guidelines comment that targeting a value of at least 10 mm Hg and ideally $\geq$20 mm Hg may be useful, whereas the 2020 pediatric guidelines state that there are no established values to guide therapy.

Limitations. Although $ETCO_2$ may be more broadly applicable to patients with cardiac arrest than invasive arterial blood pressure monitoring, there are important potential confounders impacting its use as a physiologic target. In addition to changes in minute ventilation (e.g. high ventilation rate), certain drug administration is also known to affect the ETCO2 values (e.g. decreased ETCO2 with epinephrine,[22,65,66] and increased ETCO2 with sodium bicarbonate[67,68]). Importantly, the reliability of $ETCO_2$ in patients without an advanced airway (i.e. with a laryngeal mask airway or bag-mask ventilation) is unknown.

Cerebral oximetry

Physiologic premise. The ultimate goal of CPR is survival with preserved neurofunctional status. While systemic measures of blood pressure and proxies for cardiac output are physiologically linked to cerebral perfusion, direct measurement of cerebral physiology during CPR is a highly desired goal in resuscitation science. The most well-studied means of intra-arrest neuromonitoring to date is near-infrared spectroscopy (NIRS), a non-invasive measure of cerebral regional oxygen saturation (rSO2). Similar to a pulse oximeter, NIRS emits light and uses a detector to measure how much light is absorbed versus transmitted to analyze the oxygen saturation. Whereas a pulse oximeter requires pulsatile blood flow to isolate the peripheral arterial saturation, NIRS uses different infrared wavelengths, which allows for greater tissue penetration and measures tissue oxygenation (a combination of arterial, venous, and capillary hemoglobin saturation).[69] Notably, NIRS does not require pulsatile blood flow and provides a continuous and real-time rSO2, with normal cerebral rSO2 values of approximately 70% in both adults and children,[70–72] and importantly, it can be applied quickly without interruptions to CPR.[73]

Supporting data. Cerebral rSO2 measurement via NIRS is feasible during adult OHCA and IHCA.[73–75] Multiple studies, including meta-analyses, have shown an association between higher cerebral rSO2 and ROSC.[76–79] Cerebral rSO2 at hospital arrival has also been shown to predict neurologic outcome.[80] The largest study of cerebral rSO2 during cardiac arrest, a multicenter study including 183 patients with IHCA, found that patients with ROSC and survival with favorable neurologic outcome had higher cerebral rSO2 values during CPR, and that percentage of time with cerebral rSO2 greater than 50% throughout CPR was the best predictor of favorable neurologic outcome (each 5% increase in the percentage of time with cerebral rSO2 >50% was associated with a 15% higher probability of favorable neurologic outcome).[81] Interestingly, in an OHCA study of 100 patients with cerebral rSO2 and $ETCO_2$ measurements, both rSO2 and $ETCO_2$ measurements were higher in patients with ROSC, but rSO2 and $ETCO_2$ poorly correlated with each other (with diagnostic accuracy of rSO2 being more specific and $ETCO_2$ more sensitive).[82]

In pediatric patients with OHCA, a small observational study observed an abrupt increase in rSO2 in all 3 patients with ROSC and found that patients without ROSC had

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lower minimum cerebral rSO2 values.[83] In pediatric IHCA, one small single-center observational study found that higher cerebral rSO2 was associated with higher rates of ROSC,[84] and a larger multi-center observational study found that higher cerebral rSO2 was associated with ROSC, survival to hospital discharge, and survival with favorable neurologic outcome.[85]

Limitations. As rSO2 represents a composite value from arterial, venous, and capillary blood, there are no normative thresholds established in baseline physiologic states or in the setting of brain injury. Correlation between rSO2 and invasively measured brain tissue oxygenation has been inconsistent.[86] Values and changes are non-specific and could represent pathophysiologic processes in the brain or non-cerebral tissues.[87] Although there is an association between higher rSO2 and outcomes, specific targets or cutoffs have yet to be established. Studies evaluating the association between cerebral rSO2 and CPR quality are needed.

Cardiac ultrasound/echocardiography

Physiologic premise. Both cardiac point-of-care ultrasound (POCUS) (or transthoracic echocardiography [TTE] and transesophageal echocardiography [TEE]) may be used during CPR for identification of reversible causes of arrest, determination of underlying cardiac activity, and optimization of CPR technique. More recently, point-of-care focused TEE has become increasingly used in critical care and emergency medicine applications, including the evaluation of circulatory shock, investigation of unexplained hypoxemia, and during cardiac arrest care. While TEE has so far largely been studied during IHCA or ED-based resuscitation care, it has been proposed for pre-hospital care during OHCA as well.[88] An advantage of TEE is that it can obtain acoustic windows that may otherwise be obscured by certain patient factors (e.g. body habitus, pulmonary disease, and gastric distension),[89] and importantly, TEE does not require access to the chest wall, thus images can be obtained during active CPR.

Supporting data. Echocardiography is useful as a diagnostic tool in identifying reversible causes of cardiac arrest (e.g. cardiac tamponade, thrombosis (cardiac or pulmonary), hypovolemia, and tension pneumothorax).[90–94] In a feasibility study, TEE yielded a number of actionable findings, including recognition of fine ventricular fibrillation (VF) that otherwise appeared electrically as asystole, recognition of significant right ventricular dilation suggestive of pulmonary embolism, and in one case the finding of intra-cardiac thrombus.[92]

In a multicenter prospective observational study, when used, TEE resulted in clinical management changes in approximately half of OHCA events and one-third of IHCA events.[94] Multiple algorithms have been proposed to incorporate echocardiography into advanced life support algorithms to identify reversible causes of arrest in adults[90,95–97] and children.[98] However, it is important to note that cardiac POCUS/TTE is associated with longer CPR pause duration.[99,100] Although feasibility studies have demonstrated that TEE can be quickly introduced and safely performed during cardiac arrest,[92,101] TEE requires specialized training. The most recent adult and pediatric guidelines both support that when there are providers with appropriate training and experience with ultrasound/echocardiography, it is reasonable to supplement standard resuscitation practices, including identification of reversible causes of arrest, but that the potential downside of interrupting chest compressions and lack of established benefit should be considered.[2,3]

Cardiac ultrasound can also be used to detect underlying cardiac activity. In patients with non-shockable rhythms, the presence of cardiac activity on ultrasound has been found to be associated with ROSC and survival outcomes.[91,96,102,103]

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However, it is notable that the absence of cardiac activity alone does not reliably predict death and thus should not be the only factor in determination of termination of resuscitation.[103,104]

More recently, echocardiography has been used to optimize of CPR technique (i.e. identifying the area of maximal compression and whether the left ventricular outflow tract is obstructed by ongoing chest compressions).[92,105–107] For example, 2 studies found that TEE could identify chest compression over the left ventricular outflow tract. The obstruction to systemic blood flow resulted in poor physiologic response to compressions that necessitated movement of hand position.[92,106] One study of TTE found that $ETCO_2$ increased significantly after cardiac ultrasound-guided hand position modifications.[108] Laboratory work in a swine model of cardiac arrest confirmed that such hand position adjustment based on TEE improved hemodynamics and yielded a higher rate of initial survival.[109] Whether TEE could offer opportunities to adjust rescuer hand position and improve survival during clinical resuscitation care remains a key knowledge gap.

Limitations. Cardiac POCUS/TTE and TEE both require specialized training for both image acquisition and interpretation, limiting their general use. Importantly, there is no current evidence that intra-arrest echocardiography improves outcomes, while cardiac POCUS/TTE is associated with longer CPR pauses[99,100] and TEE poses risk of bleeding and esophageal rupture. Notably, there is also a potential for misinterpretation of findings. Whether TEE can allow for continuous measurement of cardiac output to adjust CPR performance metrics, such as rate and depth of compressions, remains to be definitively established.

Pulse oximetry plethysmography

Physiologic premise. Pulse oximeters are ubiquitous, non-invasive monitors that can be easily applied and interpreted in both the pre-hospital and in-hospital settings (including outside of the intensive care unit), where other physiologic markers of CPR quality (i.e. invasive arterial blood pressure and $ETCO_2$) may be unavailable. Although the primary use of a pulse oximeter is to measure peripheral oxygen saturation, the waveform itself is indicative of perfusion.[110,111] Characteristics of the pulse oximeter waveform, including amplitude and area under the curve (AUCp) may be useful as indicators of CPR quality and predictors of ROSC.

Supporting data. Animal studies have shown that the pulse oximeter reliably detects chest compression rate and CPR pauses,[112,113] the amplitude and AUCp correlate with invasive markers of CPR quality (i.e. CoPP and $ETCO_2$),[113] and pulse oximetry can be used to detect ROSC during active CPR.[114,115] In one study, a machine learning-based algorithm was able to use the electrocardiogram (ECG) and photoplethysmography to estimate CoPP, which correlated with invasive measures of CoPP.[116] In a prospective multicenter study of both OHCA and IHCA patients, the pulse oximeter plethysmography amplitude and AUCp during CPR were higher in patients who achieved ROSC than those who did not and had similar ability to predict ROSC compared to $ETCO_2$ early in the resuscitation, but not later in the resuscitation or throughout the entire resuscitation.[117]

Limitations. Although the ubiquitous applicability of the pulse oximeter presents an exciting opportunity for physiologic-directed CPR in all patients with cardiac arrest both in and out of the hospital, significant knowledge gaps remain including how to interpret and implement this technology in real-time to improve CPR quality and outcomes.

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Electrocardiogram/ventricular fibrillation waveform

Physiologic premise. ECG waveform analysis has been foundational in managing ventricular arrhythmias during resuscitation since the introduction and standardization of external cardiac defibrillation in the 1960s. Beyond simple recognition of a "shockable" rhythm, quantitative analysis of VF waveform characteristics provides insight into myocardial physiology and metabolism, and thus, the likelihood of defibrillation success. The most well-established quantitative VF waveform metric is an energy intensity estimate known as Amplitude Spectrum Area (AMSA), which incorporates data regarding both the amplitude and frequency of the VF waveform. Utilizing machine learning models, AMSA can be generated and applied in real-time.

Supporting data. In an observational study of adult OHCA, AMSA was significantly higher (AMSA $\geq$15.5 mV-Hz had a positive predictive value of 84%) prior to successful defibrillation, as well as sustained ROSC and long-term survival. Conversely, AMSA $\leq$6.5 mV-Hz had a negative predictive value of 98% for defibrillation success.[118] Similar findings have been replicated in other observational studies[119] and more recent retrospective, multicenter data similarly showed lower AMSA values were independently associated with higher risk of death and poor neurologic outcome at 30 d and 1-y post-arrest.[120] A clinical trial of immediate defibrillation versus defibrillation timing based on waveform analytics failed to demonstrate differences in outcomes,[121] while another trial incorporating AMSA into defibrillation strategy was stopped early due to the COVID-19 pandemic.[122] Recent advances to reduce CPR-induced artifact enhance determination of changes in AMSA during active CPR,[123,124] which could facilitate continuation of uninterrupted, high-quality CPR when defibrillation has a low-predicted probability for success per real-time AMSA feedback. Additionally, an observational study demonstrated that AMSA could facilitate lower energy defibrillation attempts with similar rates of successful defibrillation, thus mitigating myocardial injury from higher energy shocks.[125] Additionally, a retrospective study found that both $ETCO_2$ and AMSA were independently associated with shock success and ROSC, and that when combined, their discriminative power significantly increased.[126] This highlights that the future of physiology-directed resuscitation will likely be led by not 1 individual physiologic marker, but by collective data regarding the patient's physiologic state.

General Framework for Physiologic Monitoring During Cardiopulmonary Resuscitation

While endorsement of a comprehensive physiology-directed CPR protocol requires more rigorous evidence, current literature and resuscitation guidelines support the incorporation of physiologic monitoring into cardiac arrest management. A general framework for the utility of physiologic monitoring during CPR is presented in **Fig. 2**. Broadly, clinicians can utilize physiologic data to: (1) verify or ensure that high-quality CPR is being delivered and rectify areas for improvement; (2) replace standard practices with more reliable measurements (e.g. arterial BP assessment rather than manual pulse checks); (3) diagnose and act upon etiologic contributors to physiologic observations (e.g. low-$ETCO_2$ despite high-quality CPR could represent an intervenable pulmonary embolus); (4) consider the prognostic implications of physiologic observations; and (5) perform physiology-directed CPR.

The Future of Physiology-directed Cardiopulmonary Resuscitation

Physiology-directed CPR represents a paradigm shift from a standardized, algorithmic, and rescuer-focused approach to cardiac arrest toward a precision-based

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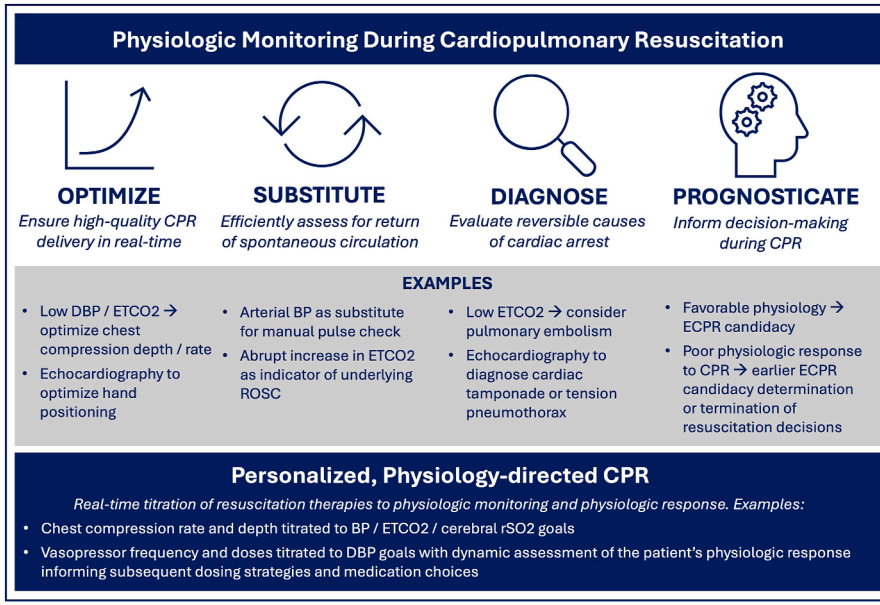
Physiologic Monitoring During Cardiopulmonary Resuscitation
OPTIMIZE
Ensure high-quality CPR delivery in real-time
SUBSTITUTE
Efficiently assess for return of spontaneous circulation
DIAGNOSE
Evaluate reversible causes of cardiac arrest
PROGNOSTICATE
Inform decision-making during CPR
EXAMPLES
Low DBP / ETCO2 → optimize chest compression depth / rate
Echocardiography to optimize hand positioning
Arterial BP as substitute for manual pulse check
Abrupt increase in ETCO2 as indicator of underlying ROSC
Low ETCO2 → consider pulmonary embolism
Echocardiography to diagnose cardiac tamponade or tension pneumothorax
Favorable physiology → ECPR candidacy
Poor physiologic response to CPR → earlier ECPR candidacy determination or termination of resuscitation decisions
Personalized, Physiology-directed CPR
Real-time titration of resuscitation therapies to physiologic monitoring and physiologic response. Examples:
Chest compression rate and depth titrated to BP / ETCO2 / cerebral rSO2 goals
Vasopressor frequency and doses titrated to DBP goals with dynamic assessment of the patient's physiologic response informing subsequent dosing strategies and medication choices

Fig. 2. Conceptual Model of Physiology-directed CPR: Conceptual model of how physiologic data can be utilized to optimize CPR quality, substitute for standard assessment practices, diagnose contributing factors, and prognosticate to inform intra-arrest decision-making to provide personalized care based on individual cardiac arrest physiology.

strategy that tailors interventions to an individual patient's physiologic response. There is strong physiologic premise for such strategies and, as detailed earlier, mounting data associating physiologic measurements during CPR with meaningful outcomes. However, despite these associations, how best to act on real-time physiologic data during CPR to improve outcomes remains unknown. The next frontier of resuscitation science must focus on translating these associations into actionable, evidence-based interventions through rigorous clinical trials. Potential approaches worthy of investigation include:

1. *Adjustment of CPR mechanics based on real-time DBP or $ETCO_2$ measurements*: Observational studies and preclinical laboratory trials have demonstrated that changing chest compression rate and depth can raise DBP and $ETCO_2$.[25,53] As noted earlier and in **Fig. 2**, low DBP or $ETCO_2$ should likely trigger resuscitation teams to check that chest compressions of appropriate rate, depth, and release velocity are being delivered. But whether teams should deviate from guideline-recommended chest compression goals in response to physiologic measurements and how those mechanics should be titrated requires prospective study.
2. *Hemodynamic-directed epinephrine administration*: Epinephrine is universally recommended during cardiac arrest to augment systemic vascular resistance, thereby increasing DBP and CoPP to enhance the likelihood of ROSC. Epinephrine is administered at a universal dose and at set intervals of every 3 to 5 min, but the optimal dose or dosing frequency is not known and likely varies between individuals. In laboratory studies of hemodynamic-directed CPR wherein epinephrine was given when and only when CoPP or DBP was below an *a priori* threshold, the number and frequency of epinephrine doses varied, and hemodynamics and outcomes were superior compared to standard epinephrine dosing.[32–36] Such an

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approach holds promise in clinical practice, but numerous questions remain outstanding. Should a patient with a DBP consistently above goal receive no epinephrine at all? What frequency of epinephrine is reasonable for a persistently low DBP? Do statistically derived physiologic cut points from observational studies translate to appropriate clinical goals, or should we aim even higher?

3. *Further personalization of vasopressor strategies*: While titration of epinephrine to an evidence-based threshold represents a step toward precision medicine, recent laboratory and clinical studies have identified considerable inter-individual heterogeneity in the physiologic response to epinephrine.[24,127,128] Specifically, some patients demonstrate a robust increase in DBP following epinephrine administration while others exhibit no response at all. In a pediatric IHCA study, greater magnitude of the DBP response to epinephrine was associated with superior outcomes. Thus, a more "personalized" approach could incorporate an individual patient's response to epinephrine to drive subsequent vasopressor decisions rather than aiming for a threshold with repeated doses. Perhaps a patient with a poor physiologic response to epinephrine requires a higher dose. Conversely, avoidance of further epinephrine when the first dose fails to achieve the intended physiologic effect may mitigate potential deleterious side effects.[129–131] Given differing mechanisms of action,[132] choosing an alternative vasoactive medication, such as vasopressin, may hold promise in such a scenario.[128,133]
4. *Integration of real-time physiology with other patient data*: Particularly in the in-hospital setting, clinical teams have a plethora of information regarding their patients' pre-arrest state. Underlying illnesses, the cause of arrest, pre-arrest exposure to vasoactive medications and mechanical ventilation, and numerous other factors impact intra-arrest physiology and should be incorporated into how intra-arrest data are interpreted and what therapies are provided.

Technologic and Practical Considerations: The feasibility, training implications, and technologic considerations for such approaches to CPR are largely unknown and vary substantially between settings. A significant barrier to implementing physiology-directed CPR is the difficulty of interpreting and acting upon multiple streams of physiologic data in real time. As clinicians managing cardiac arrest already face high cognitive loads, expecting them to consider arterial blood pressure, $ETCO_2$, cerebral oximetry, and other physiologic signals during resuscitation efforts may not always be practical. Human and system factors, team dynamics, and training implications require rigorous investigation in and of themselves. Ideally, widespread implementation of physiology-directed CPR will be accompanied by the deployment of technology to continuously integrate physiologic signals, summarize measurements and trends, and provide decision support to clinicians.

SUMMARY

Invasive arterial blood pressure and $ETCO_2$, among other physiologic measures, are now well-established to be associated with clinically important cardiac arrest outcomes. In current state, these physiologic data can be used to monitor and perhaps improve upon resuscitation performance. Physiology-directed CPR represents a promising shift toward precision resuscitation by tailoring therapy to individual patient responses measured through real-time physiologic monitoring. However, significant barriers impede widespread clinical adoption. Rigorous prospective trials are required to determine optimal physiologic targets, demonstrate clinical efficacy, and develop accessible decision-support systems to fully realize the potential of physiology-directed CPR for improving cardiac arrest survival and neurologic outcomes.

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CLINICS CARE POINTS

- Current CPR guideline-recommended targets are provider-centric and importantly do not adapt in real-time based on patient physiologic response
- Physiology-guided CPR represents a shift toward precision resuscitation, aiming to optimize survival and neurologic outcomes by adapting CPR techniques in real-time based on individual patient physiology.
- Key physiologic markers, including arterial blood pressure and $ETCO_2$, are associated with ROSC, survival, and neurologic outcomes; specific targets and practical implementation strategies remain key knowledge gaps.

DISCLOSURES

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